M17-05 Novel Vaccines and Immunotherapy, Thur, Sept 6, 10:30 - 12:00

MAGE-A3 vaccine

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Surgical resection is the standard approach for patients with early stage NSCLC. Even after complete resection, about half of these patients will relapse and die within 5 years. Cisplatin-based adjuvant chemotherapy has been proven to improve the prognosis for patients with resected stages II, IIIA and perhaps some IB [1]. In the LACE meta-analysis, the pooled hazard ratio was 0.89 (95% CI 0.82-0.96), translating into a 6% benefit in 5-year survival (from 43 to 49%) with adjuvant chemotherapy [2]. Postoperative administration of Cisplatin-based chemotherapy, however, often results in substantial toxicity, especially after pneumonectomy, and quite some patients are not able to receive it because of co-morbidity or postoperative problems [3]. Effective and better tolerated adjuvant strategies are therefore most welcome.

Cancer immunotherapy might be a good candidate to achieve this goal. In a broad sense, cancer immunotherapy is stimulation of the immune system to treat cancer. This can be supportive (non-specific enhancement of innate immune system), passive (supply immune response to the system by giving antibodies or cytotoxic T cells), or active by specific priming of the immune system to recognize the tumor as foreign. Only the last one is *cancer vaccination* in its true sense.

Conditions for optimal cancer vaccination are: 1/ specificity (i.e. having a well defined target antigen in the tumour, not in other tissues); 2/ selectivity (i.e. used in the population expressing the target); 3/ interaction with antigen leads to (more) effective humoral and/or cellular response; 4/ tumour must be sensitive to immune killing in order to obtain improvement in patient outcome.

A recently reported phase II randomised study with postoperative vaccination with the MAGE-A3 vaccine in patients with completely resected non-small cell lung cancer (NSCLC) has to be seen in this perspective [4].

The postoperative MAGE-A3 approach meets quite some of the conditions listed above. The MAGE-A3 gene is expressed specifically in tumour cells with no expression in normal cells (specificity). MAGE-A3 is significantly expressed in NSCLC, present in at least 35% of intra-operative samples in stages IB, II or IIIA tumours (selectivity) [5]. Pilot studies evaluating the MAGE-A3 cancer immunotherapeutic demonstrated humoral and cellular responses, and long-lasting clinical objective responses in metastatic melanoma patients [6,7]. Moreover, the vaccine consists of the MAGE-A3 recombinant protein combined with a potent GSK proprietary immunological adjuvant. Therefore, postoperative immunization with the MAGE-A3 cancer immunotherapeutic may be a tumor-specific, well tolerated, and effective adjuvant therapy.

In this phase II randomised study, patients with completely resected, MAGE-A3 positive, pathological stage IB or II NSCLC were randomly assigned to postoperative intramuscular administrations of MAGE-A3 or placebo (2:1 randomisation), with 5 administrations at 3-week intervals, followed by 8 administrations every 3 months. Stratification factors included stage (IB vs. II), histology (squamous carcinoma vs. other), and lymph-node procedure (minimal lymph-node sampling vs. radical mediastinal lymphadenectomy). The primary endpoint was disease-free interval; secondary endpoints were safety, disease-free survival, and overall survival.

A total of 1089 surgical tumour specimens were examined by rt-PCR, of which 363 expressed the MAGE-A3 gene. Between 01/2002 and 05/2004, 182 patients (122 stage IB, 60 stage II) from 59 centres in 14 European countries were randomised. The median age was 63 (45-81), 87% were males, pathology was 65% squamous cell carcinoma. After a median follow-up of 28 months, 67 recurrences were observed. Group comparisons of disease-free interval, disease-free survival, and overall survival gave respectively a hazard ratio of 0.74 (95%CI 0.44-1.20, p=0.107), 0.73 (95%CI 0.45-1.16, p = 0.093) and 0.66 (95%CI 0.36-1.20, p = 0.088) in favour of the MAGE-A3 group. Overall, treatment was well tolerated, with only 3 grade 3 adverse events possibly related to the treatment.

As whole, MAGE-A3 cancer immunotherapeutic as adjuvant treatment in completely resected Stage IB or II NSCLC was a targeted, well tolerated postoperative therapy, with a positive signal for clinical activity in the phase II randomised setting (relative improvement in disease-free interval and disease-free survival 27%). Further Phase III evaluation in early NSCLC is planned for 2007.

References

(1) Vansteenkiste JF, Schildermans RH. The future of adjuvant chemotherapy for resected non-small cell lung cancer. *Expert Rev Anticancer Ther* 2005;5:165-175.

(2) Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung Adjuvant Cislatin Evaluation (LACE): A pooled analysis of five randomized clinical trials including 4564 patients. J.Clin.Oncol. 24, 366S. 2007 (abstract).

(3) Kassam F, Johnston MR, Feld R, Shepherd F, Darling G, Keshavjee S, et al. Referral patterns for adjuvant therapy in non-small cell lung cancer. J.Clin.Oncol. 23, 674S. 2007 (abstract).

(4) Vansteenkiste J, Zielinski M, Dahabre J, Linder A, Malinowski W, Jassem J, et al. Multi-center, double-blind, randomized, placebo-controlled phase II study to assess the efficacy of recombinant MAGE-A3 vaccine as adjuvant therapy in stage IB/II MAGE-A3-positive, completely resected non-small cell lung cancer (NSCLC): final results. Proc.ASCO. 2007 (abstract).

(5) Sienel W, Varwerk C, Linder A, et al. Melanoma associated antigen (MAGE)-A3 expression in stages I and II non-small cell lung cancer: results of a multi-center study. *Eur J Cardiothorac Surg* 2004;25:131-134.

(6) Marchand M, Punt CJ, Aamdal S, et al. Immunisation of metastatic cancer patients with MAGE-3 protein combined with adjuvant SBAS-2: a clinical report. *Eur J Cancer* 2003;39:70-77.

(7) Kruit WH, Van Ojik HH, Brichard VG, et al. Phase 1/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma. *Int J Cancer* 2005;117:596-604.

Session M18: Hot Issues in the Management of Brain Metastases

M18-01 Hot Issues in the Management of Brain Metastases, Thur, Sept 6, 10:30 - 12:00

Whole brain radiotherapy and stereotactic radiosurgery for brain metastases from NSCLC

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Brain metastases are a common complication of advanced stage non-small cell lung cancer (NSCLC), with an estimated incidence at initial diagnosis of 10-20%, increasing to up to 40% in the two years following diagnosis [Carolan 2005]. Palliative whole brain radiotherapy (WBRT) has been the mainstay of treatment for patients with multiple brain metastases, extending survival to 3-6 months. However, despite

WBRT approximately 50% of patients die with symptoms of intracranial progression. Attempts to increase the treatment efficacy by dose-escalation of WBRT [Murray 1997], or by focal radiation dose increase [Hoskin 1990], have proven unsuccessful. Similarly, the concurrent use of radiation sensitizers has failed to result in improved outcome of WBRT. Recent studies have focussed on the tolerability and efficacy of the combination of WBRT and chemotherapy, e.g. with temozolomide, gefitinib and erlotinib. However, thus far randomized phase III studies are lacking for most chemotherapeutic agents, and available data are mostly from phase I/II studies.

Stereotactic radiosurgery (SRS) is characterized by the high-precision delivery of a single fraction of high-dose radiotherapy. SRS techniques generate a rapid dose fall-off outside the target volume, thereby sparing the normal brain tissue and allowing for high biologically equivalent doses to be precisely delivered. SRS is generally considered to be the preferred treatment for patients with a limited number (1-3) of brain metastases in any location of the brain, including the brainstem. Several published series have shown that SRS is highly effective in both single and multiple brain metastases, with local control rates of 70-90% and median survival rates of between 6 and 12 months being reported. The superiority of SRS over WBRT, however, has only been demonstrated for patients with a single brain metastasis. A randomized trial has been performed by the RTOG, where 333 patients with 1-3 brain metastases were assigned to WBRT alone or WBRT plus SRS [Andrews 2004]. The overall trial failed to show a significant improvement in median overall survival, but patients with a single metastasis had improved survival (6.5 vs. 4.9 months, p=0.05) and functional autonomy after WBRT and SRS.

Although a randomized comparison between neurosurgery and radiosurgery is lacking, the results of both approaches are comparable and SRS is considered to be a non-invasive alternative to surgery, with less morbidity and mortality. In recent years, neurosurgery generally has been reserved for space-occupying lesions with a diameter of >3 cm, and for cases where pathological confirmation is required.

Whether SRS should be delivered as a sole modality or in combination with WBRT for primary brain metastases remains a controversial issue. The rate of development of new brain metastases after SRS is dependent on the number of brain metastases treated, but also on the quality of pre-treatment imaging as high-resolution, double-contrast MRI scans can detect additional small metastases in a considerable number of patients. A multi-institutional study [Sneed 2002] showed that the upfront addition of whole brain radiotherapy (WBRT) to SRS decreased the intracranial failure rate, but as a result of efficient salvage therapy, this failed to have a significant impact on the survival of patients. A recently reported randomized trial in patients with 1-4 brain metastases has confirmed the above findings [Aoyama 2006], with a 1 year actuarial rate of developing new brain metastases of 42% in the WBRT plus SRS group and 64% in the SRS-alone group (p=0.003). However, not all intracranial relapses were symptomatic and salvage therapy was required in 15% and 43% of patients after WBRT plus SRS and after SRS only, respectively. Furthermore, in the majority of patients salvage SRS could be performed, sparing patients from the potential side effects of WBRT. In the light of these findings, most authors advise to use SRS as a single modality without upfront WBRT for the primary treatment of brain metastases.

Recent years have witnessed a shift towards more aggressive treatment for patients with a synchronous presentation of NSCLC and a single brain metastasis. This approach seems particularly valuable for patients presenting with a thoracic stage I NSCLC, where combined surgical treatment of the brain metastasis and the primary tumor has resulted in survival rates that are similar to stage I patients [Billing 2001; Hu 2006]. The reported high efficacy of stereotactic body radiotherapy (SBRT) for early stage NSCLC nowadays allow for a non-invasive, but still aggressive treatment regiment in this subset of patients with combined SBRT for the primary tumor and SRS for the brain metastasis. The results of such an aggressive approach, however, were far less favourable for patients with more advanced thoracic stages.

Radiotherapy facilities for delivering radiosurgery have been increasing rapidly in recent years and the introduction of non-invasive patient immobilization techniques, e.g. the use of frameless radiosurgery have made SRS a well tolerable, patient-friendly technique that can be performed on an outpatient basis. The toxicity of SRS is only very limited with fatigue, and local alopecia being the most commonly encountered side effects.

At the VUmc Amsterdam, SRS for patients with primary or recurrent brain metastases from NSCLC has been performed since the early 1990's. Well over a hundred patients have been treated and the results of this series with respect to patterns of failure and toxicity will be presented during the meeting.

References:

Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-1672.

Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-2491.

Billing PS, Miller DL, Allen MS, et al. Surgical treatment of primary lung cancer with synchronous brain metastases. J Thorac Cardiovasc Surg 2001;122:548-553.

Carolan H, Sun A, Bezjak A, et al. Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? Lung Cancer 2005;49:109-115.

Hoskin PJ, Crow J, Ford HT. The influence of extent and local management on the outcome of radiotherapy for brain metastases. Int J Radiat Oncol Biol Phys 1990;19:111-115.

Hu C, Chang EL, Hassenbusch SJ 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 2006;106:1998-2004.

Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. Int J Radiat Oncol Biol Phys 1997;39:571-574.

Sneed PK, Suh JH, Goetsch SJ, et al. A multiinstitutional review of radiosurgery alone vs radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 2002;53:519-526.

M18-02 Hot Issues in the Management of Brain Metastases, Thur, Sept 6, 10:30 - 12:00

Brain metastases: surgery versus radiosurgery versus whole brain irradiation

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Metastasis to the brain is the most common neoplasm of the brain, occurring 25-35% of all cancer patients. Approximately one-half of these patients present with a single lesion in the brain. Treatment options for patients with single brain metastasis include whole brain irradiation (WBI), surgical resection (S), and stereotactic radiosurgery (SRS). Prospective randomized studies that compared S followed by WBI to WBI alone found that the addition of surgical resection to WBI improved local control and survival. Many studies indicated that SRS achieves local control in 80-95% of metastases. With the proven ability of SRS to achieve local control, SRS was compared with S with comparable outcomes. However, WBI alone appeared to be inferior either to SRS